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The Outstanding Beneficial Roles of Irisin in Depressive Disorders

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Abstract

Depression is a widely observed psychiatric disorder that affects a quite large number of people all around the world. A major depressive disorder (MDD) is a multifactorial disease that IS associated with fluctuations in appetite, body weight, and energy situations in addition to serious mood problems. The aim of this review is to investigate a possible link between energy regulatory hormones of irisin and depressive disorders.

Irisin is a hormone that plays a significant role in the regulation of lipid and glucose metabolism in skeletal muscle and adipose tissue.

Irisin was also reported to play significant roles in the central nervous system. In the literature there are reports indicating a beneficial antidepressant role of irisin in MDD.

It should be emphasised that the antidepressive effects of exercise could be the result of exercise-induced increased hormones of irisin.

Key words: irisin; major depressive disorders; FNDC5; type 2 diabetes mellitus; obesity

Introduction

Depression/major depressive disorder (MDD) is a disease that has genetic, biochemical, and neurophysiological causes and consequences, and is characterized by feelings such as nervousness, insecurity, hopelessness, worthlessness, and guilt. In addition,

symptoms such as decreased ability to concentrate and think, decreased or increased appetite, weight loss or weight gain, insomnia or hypersomnia, low energy, fatigue or increased agitation, decreased interest in pleasurable stimuli (anhedonia), and recurrent thoughts of death and suicide may occur. It is a mood disorder [1, 2]. In 2008, the World Health Organization stated that MDD held third place worldwide in terms of disease burden but predicted that it will be in first place by 2030 [3]. The general prevalence of MDD in society is 15%; it is one of the most common psychiatric disorders in women, with a rate of 25%. With the COVID-19 virus outbreak in 2020, these rates have increased significantly, with many researchers reporting a sudden increase in stress, anxiety, and depression and a further progression of existing psychiatric disorders [4–7]. The potential roles of energy regulatory hormones in patients with depressive disorders and neuropsychiatric function have become a topic of interest in clinical medicine [8, 9]. Irisin is a recently discovered muscle-released myokine, and its relationship with depression, as well as many other diseases, is being investigated. This review aims to examine the physiological relationship between 2 phenomena that have attracted attention, especially recently.

The history of irisin

Irisin was discovered in 2012 as a hormone released from the muscle cells of transgenic mice encoding a gene in a genomic study examining the PPARGC1A gene [10]. The Ppargc1a gene is responsible for encoding the peroxisome proliferator-activated receptor gamma coactivator 1-alpha PPAR-γ co-activator-1 α (PGC-1α) transcription cofactor, which plays a key role in various body systems [10]. In a study in the literature, when a mouse model that overexpressed PGC-1α was studied, it strongly increased the expression of fibronectin type III domain 5 (FNDC5) proteins. Later, it was understood that this myokine, which was discovered as a thermogenic protein that causes energy expenditure by turning white adipose tissue into brown adipose tissue, was actually released into the bloodstream by cleavage of the membrane protein called FNDC5 in the muscles. This proteolytic product with 112 amino acids, which is formed by the breakdown of 212 amino acid FNDC5 protein, is called “irisin”. The name irisin comes from the name 'Iris', the messenger goddess in Greek mythology [10].

Biochemical structure and secretion of irisin

Irisin is a protein-structured hormone secreted from muscle tissue, with a molecular weight of 12 kDa, containing 112 amino acids [10]. This hormone-like myokine is secreted

from skeletal muscle into circulation as a product of FNDC5 in response to exercise. FDNC5, which can also be referred to as FRCP2 or PeP protein, was first identified as a receptor in 2002, and it was stated to be critical for the differentiation of myoblasts and neurons [11, 12]. However, studies on FNDC5 remained scarce until the discovery of irisin.

The FNDC5 protein consists of a 209 amino acid primary structure, hydrophobic transmembrane domain, and a C-terminal domain, and it serves as a signal peptide [11]. The first 29 amino acids that make up the primary structure of mouse FNDC5 are a signal peptide, followed by the fibronectin III (FNIII) domain consisting of 94 amino acids, and the next 28 amino acids have unknown structure and function. This 28-amino-acid site contains the putative cleavage site for irisin. Next comes a 19-amino-acid transmembrane domain and a 39-amino-acid cytoplasmic domain. As a result, FNDC5 is a type-I transmembrane protein the FNIII domain of which is extracellular [13]. Part of the extracellular N-terminal is cleaved and released into circulation [10]. The cleavage process of irisin derived from the extracellular domain of FNDC5 and the enzymes that mediate this process have not been fully elucidated.

The structure of irisin consists of an N-terminal FNIII-like domain attached to a flexible C-terminal tail. This area forms a continuous subunit-leaf dimer that has not been seen before [14]. It was preserved throughout the evolutionary process and is 100% similar in mice and humans [10].

In addition, irisin was accepted as an exercise-dependent myokine based on the up-regulation of FNDC5 in mouse skeletal muscle after exercise [10]. Although it is mainly found in perimysium and endomysium in skeletal muscle, it was detected in heart muscle (pericardium), brain, cerebrospinal fluid, optic nerve, tongue, and rectum and, to a lesser extent, testicles (Sertoli and Leydig cells), pancreas, liver, spleen, and stomach tissues [15, 16]. In addition, due to the presence of irisin in the cerebellum, it was suggested that the cerebellum may be a neural circuit that can regulate adipocyte metabolism and connect it to adipose tissue [17].

FNDC5 is also expressed in the brain [11, 12]. Exercise induces FNDC5 in the hippocampus dependent on PGC-1α, which leads to increased BDNF expression [18, 19]. BDNF is a powerful regulator of neurogenesis, synaptogenesis, and synaptic plasticity [20]. In many studies, it was stated that exercise has beneficial effects on brain health and cognitive skills and improves results in neurological conditions such as depression, epilepsy, stroke, Alzheimer’s and Parkinson’s disease [21–25]. Accordingly, it was suggested that the molecular mediator of exercise-dependent neurogenesis may be FNDC5/irisin.

Because of its presence in many tissues, irisin, like many other molecules, is not specific and cannot be thought of as just a myokine. In addition, it was stated in a study that it also secretes FNDC5 from white adipose tissue, so the irisin is not only a myokine but also an adipokine [26, 27]. Approximately 72% of FNDC5/irisin in circulation was previously released due to muscle secretion [28]. Exercise-induced increases of circulating irisin levels have been shown in many studies [10, 29, 30]. In addition, improved depression conditions in MDD patients following exercise programs have been reported [31, 32].

Irisin's mechanism of action

Irisin is differentiated from the FNDC5 molecule, which is membrane-bound in skeletal muscle, by the trigger of exercise and muscle movements [33]. When the N-terminal part is cleaved and released as irisin, the C-terminal domain of FNDC5 remains in the cell [33]. Irisin shows its effect on white adipose tissue by stimulating brown fat-like genes, but its receptor has not yet been discovered [10]. In addition, irisin can cross the blood-brain barrier and affect the central nervous system [34].

The first mechanism of action is that after binding to the hormone receptor, it activates the cyclic adenosine mono phosphate (cAMP), protein kinase-A (PKA), and hormone sensitive lipase (HSL)/perilipin pathway, which ensures fat breakdown. Adenylate cyclase enzyme is activated first in the cell membrane, and cAMP increase occurs inside the cell. The increasing cAMP level activates PKA. PKA induces phosphorylation of both HSL and perilipin. Perilipin is a protein found on the surface of lipid droplets that reduces fat breakdown. HSL allows the stored lipid droplets to move from the cytosol in order to lipolyze perilipin. Irisin-induced down-regulation of perilipin and up-regulation of HSL increase lipolysis [35].

The second mechanism of action is that irisin stimulates the nucleus in an unknown way, increasing UCP1 expression and blocking ATP production in the electron transport system, increasing heat production. Increased heat production with the increase of UCP1 expression increases energy expenditure in terms of glucose/fat metabolism. It also provides activation of HSL [10, 35].

Physiological effects of irisin

White and brown fat cells are different from each other. While white adipose tissue stores energy as fat, brown adipose tissue distributes energy as fatty acids and accelerates

energy burning [36]. Irisin causes the white adipose tissue to convert to brown [10]. As a result of the transition from white adipose tissue to brown, fat and glucose metabolism is mainly affected. This is important because it can be associated with many metabolic disorders such as obesity and type 2 diabetes.

In addition, irisin regulates the mechanism of body temperature. In rodents, brown adipose tissue releases heat with the effect of UCP1 in thermogenesis without shivering [37]. If the heat demand cannot be met sufficiently by thermogenesis without shivering, shivering comes into play. In this way, heat begins to be produced from muscle contractions [38]. Irisin induces thermogenesis by both increasing UCP-1 expression and stimulating the browning of adipocytes. As a result, through these effects, irisin ensures energy expenditure and regulates browning of adipocytes, thermoregulation, and glucose homeostasis [10].

In addition, irisin, which is a myokine, induces genes that regulate the energy mechanism of the cell by acting on skeletal muscle, causing an increase in energy expenditure and oxidative metabolism. FNDC5 expression and release of irisin increase during myogenic differentiation in myocytes via the ERK pathway [39]; this affects the glucose metabolism by increasing glucose uptake into the muscle via GLUT4 via the AMPKα2 pathway accompanied by p38MAPK-GLUT translocation in differentiated skeletal muscle cells [39].

Direct association of irisin and depression

Different studies are still being conducted about the possible effects of irisin. Studies on FNDC5 and PGC-1α, from which irisin originates, constitute these possible effects. The hippocampus and ventral tegmental area (VTA), from which FDNC5 was seen to be released, was found to be effective on the proactive learning style (with the use of the reward signal) [40, 41]. The relationship between dopaminergic neurons of the mesolimbic system in the reward-related learning process is known [42]. These neurons play a role in the regulation of mood, motivation, reward, pleasure, and arousal by secreting dopamine [43]. Moreover, the rewarding effects of addictive pharmacological agents such as alcohol, nicotine, cocaine, and heroin are associated with mesolimbic dopaminergic neurons [44, 45].

In addition to its direct effect, BDNF, which increases the expression of FNDC5 the precursor of its irisin, also plays a role in regulating the function of dopaminergic neurons. BDNF increases the dopaminergic effect by activating the presynaptic dopamine-3 receptors in VTA and the kinase B receptor associated with tropomyosin [41]. In this way, it modulates dopamine release related to neuronal plasticity, and plays an effective role in learning and

memory [46]. Besides many other effects, mesolimbic dopamine plays an important role in the reward pathway, such as mediating severe social stresses [47].

Although it is still not known how BDNF affects the mesolimbic reward pathway, it was determined that activation of this pathway increases the amount of BDNF in the nucleus accumbens (NAc) and that CRF here mediates the stress transition [48]. Studies about the role/condition of the brain's mesolimbic circuitry in stress regulation and depression show that exposure to a single uncontrollable deterrent experience causes impairment in response to rewarding/deterrent stimuli and inhibition of dopamine release in rewards [49]. It was reported that chronic stressful experiences can reduce the ability of stressors by disrupting their behaviour, induce behavioural sensitivity to psychostimulants, and cause adaptive changes in mesolimbic dopamine function [49].

In a recently published study comparing athletes with a control group, the level of irisin was inversely correlated with mild depression and low-grade white matter lesions in the brain [50]. However, a study performed in obese women showed no association with depressiveness and plasma irisin levels [51].

The role of irisin in the physiopathology of depression

In order to understand the role of irisin in the pathophysiology of depression, the physiopathology of depression should be examined first. Although there are several theories about this, it is still not fully elucidated. These theories are largely based on the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and the hippocampus, and include neurotransmitters such as corticotropin-releasing hormone (CRH), glucocorticoids, brain-derived neurotrophic factor (BDNF), and dopamine [52].

Stress, particularly interpersonal stress, is one of the strongest proximal risk factors for depression [53]. In depressed individuals, profound differences in behaviour may occur with the onset of symptoms such as sad mood, anhedonia, decreased motivation, decreased energy level, fatigue, and social-behavioural withdrawal [47, 53]. The physiological mechanism of these behavioural changes and its relationship with irisin was investigated in many different studies.

In one study, anhedonia, one of the main symptoms of major depressive disorder (MDD), was associated with decreased sensitivity to reward [54]. In addition, Wu et al. reported that the hypermetabolism of BDNF may be a function of anhedonia rather than other features in MDD in a study comparing MDD patients with and without anhedonia [55].

In a study investigating social withdrawal/non-communication (another symptom of MDD), mice exposed to repetitive aggression displayed reluctance for social communication, and BDNF was necessary for this response [56].

In a study in the literature involving stroke patients, low serum irisin level was found to be associated with post-stroke depression (PSD) [57]. In another study with bronchial asthma patients, distress disorder (a general term that includes MDD), which is the most well-known comorbidity of bronchial asthma, was found in very few/no patients with higher serum irisin and BDNF [58]. According to these data, a high serum irisin level decreases the risk of developing MDD.

The therapeutic effect of irisin on depression

In addition to the MDD physiopathological role of irisin, its therapeutic effects were also investigated. Irisin injections were given to rats with chronic unpredictable stress. As a result of this application, irisin regulated energy metabolism in the prefrontal cortex of the brain and exerted antidepressant-like effects in rats [59]. Antidepressants work with the principle of increasing BDNF expression and preventing stress-induced BDNF decrease by increasing BDNF mRNA through 5-HT2A and β-adrenoceptor subtypes. Neurotrophic factors such as BDNF or neurotrophin-3 (NT-3) increased the function of 5-HT-containing neurons in the rat brain and stimulated their growth [60]. In terms of increasing BDNF expression, irisin shows similar effects, using a similar pathway to antidepressant drugs.

Various studies were conducted on this with different patient populations. As a result of the high rate of depression in post-operative patients, irisin treatment was used in one study. It was reported that irisin reduces depressive symptoms in mice exposed to propofol used for general anaesthesia, inhibits propofol-induced neuronal cell death, and inhibits cytokine release from astrocytes [61]. In addition, epidermal growth factor receptor (EGFR), which is proven to play a role in the pathogenesis and progression of different cancer types, was reported to reduce the propofol-dependent increase in surface expression [61, 62]. In a study in the literature, mice were injected with central irisin. Likewise, an antidepressant-like effect was achieved. In addition, it was reported to enhance the expression of PGC-1α mRNA (which controls mitochondrial biogenesis and oxidative metabolism) in the hippocampus and prefrontal cortex [63, 64]. PGC-1α also acts as a potent ROS removal regulatory antioxidant by increasing the expression of many ROS detoxifying enzymes, and it appears to be associated with prevention of neurodegenerative disorders such as aging [63]. This effect is

also important in terms of the risk of MDD development; various experimental protocols in humans and animals showed that inflammation and neuroinflammation combined with external stimuli and neurophysiological mechanisms can trigger the formation of MDD [65]. Increasing the expression of PGC-1α decreases both the synthesis and release of proinflammatory cytokines and glutamatergic neurotoxicity [65].

There are many studies in the literature about the relationship between MDD and physical exercise that secretes irisin. In a study conducted on patients with mild/moderate MDD, physical exercise had an antidepressant-like therapeutic effect [66]. In another study, moderate aerobic exercise was performed by MDD patients for 8 weeks; while cognitive improvements were observed in the patients, it was reported that depression scores decreased [67]. In addition, in a study comparing healthy individuals and MDD patients, subjects exercised and hippocampal activity was examined by neuroimaging methods. Exercise was found to promote neuroplasticity in both healthy and depressed brains [68]. In addition, it can increase neuronal efficiency in individuals with low compliance and cause a great mood change in patients with MDD [68]. However, contrary to the literature, in a study conducted on obese women, irisin was not associated with depression, anxiety, perceived stress level, and eating disorders [51].

Some studies reported that exercise has antidepressant-like effects. However, the mechanisms mediating this effect have not been fully explained. Possible mechanisms of action such as reducing neuroinflammation and peripheral inflammation and affecting the reward pathway in the mesolimbic cerebral were emphasized [69]. Some studies show that physical exercise promotes changes in the monoaminergic neurotransmission circuit, one of the main mechanisms of MDD and antidepressant treatments, through its effect on the release of proinflammatory cytokines [65, 70].

With recent advances, researchers examined the FNDC5 C-terminal and irisin fragment to explain this mechanism. In a study, immunohistochemical analyses and staining were performed in all hippocampal areas in mice that underwent a physical exercise protocol. There was an increase in cell proliferation, neuronal differentiation, and neuronal survival in the dorsal and ventral dentate gyrus. In addition, the duration of immobility, one of the depressive symptoms, was reduced in mice. Finally, exercise also increased the number of FNDC5-positive cells in the hippocampal dentate gyrus and the immune content of FNDC5 C-terminal and FNDC5/irisin in the whole hippocampus. The FNDC5 C-terminal fragment/irisin pathway was reported to have an antidepressant-like, pro-neurogenic, and

neuroprotective effect through treadmill running [71]. The dentate gyrus is the hippocampal area responsible for the regulation of cognitive and emotional behaviour [72]. Therefore, the increase of FNDC5/irisin in this area indicates that irisin may be effective in regulating emotional behaviour. In addition, it was suggested that the beneficial effects of physical exercise on MDD are likely to be mediated by the FNDC5/irisin pathway.

Possible relationship between irisin and depression

Due to the effects of irisin on glucose and lipid metabolism, the situation in many diseases is a topic of curiosity for many researchers and has been the subject of many studies. It was suggested that irisin, which is introduced with the “sport in the pill” discourse, can provide many of the positive effects of sports on health in a short time [10]. First of all, it was seen as a promising solution for diseases such as obesity and type-2 diabetes mellitus (T2DM) and was the subject of research. Considering that the most common diseases accompanied by depression are obesity and T2DM, a possible relationship should be examined.

Obesity, depression, and irisin

Although obesity and MDD are very common, the physical and psychiatric conditions, causal pathways, or mechanisms that link them have not yet been elucidated [73, 74]. In addition to studies suggesting that obesity causes MDD, there are studies reporting that the negative treatment of MDD triggers obesity or that they occur concurrently [74–76]. Although there are different theories about underlying factors, it was reported in the literature that there is a significant positive relationship between these 2 diseases with a high prevalence [77–79]. It would also be useful to look at the relationship between exercise, irisin, and depression in terms of obesity.

In many studies, it was found that the irisin levels of obese people are significantly reduced in terms of circulating irisin levels compared to healthy individuals [26, 80].

Some studies suggested that muscle FNDC5 gene expression in humans increased with obesity, and it was reported that irisin decreased as a result of weight loss after bariatric surgery [15, 81]. However, Huh et al. also reported that this relationship may be a compensatory mechanism [15].

Although there are many studies in the literature that examine the relationship between MDD and irisin, and obesity and irisin, there is no study that compares the relationship between MDD, obesity, and irisin, which progresses with common mechanisms.

Type 2 diabetes mellitus, depression, and irisin

A similar relationship to the obesity/MDD relationship is seen between T2DM and MDD. They have identical mechanisms feeding each other and are mutually seen as risk factors [82–84].

Contrary to studies on obesity, a study by Duran et al. found no relationship between irisin levels and body mass index. It was reported that irisin is a myokine that gradually decreases with the formation of glucose intolerance and the progression of T2DM [85]. These data were supported in many other studies; it was found that FNDC5 mRNA decreased in patients with T2DM [26] and that irisin decreased significantly [86–88].

In a study conducted in patients diagnosed with T2DM and mild cognitive impairment, the level of irisin in plasma correlated with cognitive impairment (especially executive function) in T2DM patients. Based on these results, researchers claimed that high irisin levels in plasma cause clinical early cognitive deficits in patients with T2DM [89].

However, there is no study in the literature examining the relationship between T2DM, MDB, and irisin comparatively, as in obesity.

Conclusions

Irisin may have undeniable therapeutic potential on depressive disorders. However, more clinical studies investigating the association of irisin and its effects on depression are required.

Conflict of interest

The authors have no conflicts of interest to declare.

Authors' contributions

All the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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